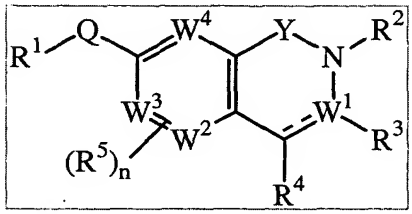
CLAIMS

What is claimed is:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is independently selected from:

C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_5 or C_6 cycloalkyl-(C_1-C_8 alkylenyl);

C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_8-C_{10} bicycloalkyl-(C_1-C_8 alkylenyl);

5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobicycloalkyl-(C_1-C_8 alkylenyl);

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;

5- or 6-membered heteroaryl;

Substituted 5- or 6-membered heteroaryl;

8- to 10-membered heterobiaryl; and

Substituted 8- to 10-membered heterobiaryl;

R^2 is independently selected from:

H;

C_1-C_6 alkyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);

8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);

Phenyl-O-(C_1-C_8 alkylenyl);

Substituted phenyl-O-(C_1-C_8 alkylenyl);

Phenyl-S-(C_1-C_8 alkylenyl);

Substituted phenyl-S-(C_1-C_8 alkylenyl);

Phenyl-S(O)-(C_1-C_8 alkylenyl);

Substituted phenyl-S(O)-(C_1-C_8 alkylenyl);

Phenyl-$S(O)_2$-(C_1-C_8 alkylenyl); and

Substituted phenyl-$S(O)_2$-(C_1-C_8 alkylenyl);

Each substituted R^1 and R^2 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

C_1-C_6 alkyl;

CN;

CF_3;

HO;

(C_1-C_6 alkyl)-O;

(C_1-C_6 alkyl)-$S(O)_2$;

H_2N;

$(C_1\text{-}C_6$ alkyl)-N(H);

$(C_1\text{-}C_6$ alkyl)$_2$-N;

$(C_1\text{-}C_6$ alkyl)-C(O)O-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)O-(1- to 8-membered heteroalkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)-C(O)N(H)-(1- to 8-membered heteroalkylenyl)$_m$;

$H_2NS(O)_2$-$(C_1\text{-}C_8$ alkylenyl);

$(C_1\text{-}C_6$ alkyl)-N(H)S$(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

$(C_1\text{-}C_6$ alkyl)$_2$-NS$(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

3- to 6-membered heterocycloalkyl-$(G)_m$;

Substituted 3- to 6-membered heterocycloalkyl-$(G)_m$;

5- or 6-membered heteroaryl-$(G)_m$;

Substituted 5- or 6-membered heteroaryl-$(G)_m$;

$(C_1\text{-}C_6$ alkyl)-S$(O)_2$-N(H)-C(O)-$(C_1\text{-}C_8$ alkylenyl)$_m$; and

$(C_1\text{-}C_6$ alkyl)-C(O)-N(H)-S$(O)_2$-$(C_1\text{-}C_8$ alkylenyl)$_m$;

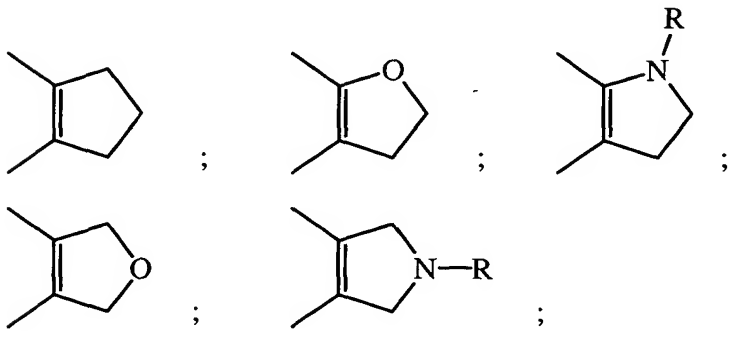
wherein each substituent on a carbon atom may further be independently selected from:

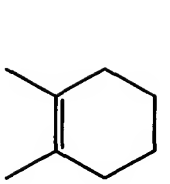
Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

wherein two adjacent, substantially sp^2 carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:

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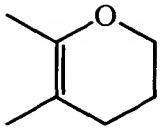
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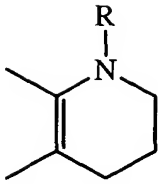
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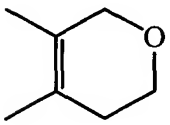
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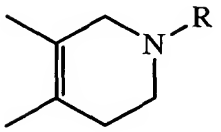
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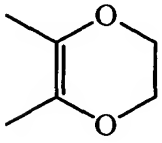
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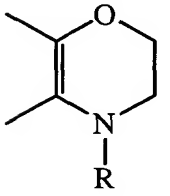
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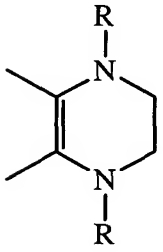
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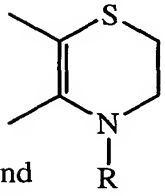
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R is H or C_1-C_6 alkyl;

G is CH_2; O, S, S(O); or $S(O)_2$;

Each m is an integer of 0 or 1;

R^3 and R^4 are independently selected from the groups:

H;

C_1-C_6 alkyl;

Substituted C_1-C_6 alkyl;

C_2-C_6 alkenyl;

Substituted C_2-C_6 alkenyl;

C_2-C_6 alkynyl;

Substituted C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

Substituted C_3-C_6 cycloalkyl;

C_3-C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Substituted C_3-C_6 cycloalkyl-(C_1-C_8 alkylenyl);

Phenyl;

Substituted phenyl;

Phenyl-(C_1-C_8 alkylenyl);

Substituted phenyl-(C_1-C_8 alkylenyl);

Naphthyl;

Substituted Naphthyl;

Naphthyl-(C_1-C_8 alkylenyl);

Substituted naphthyl-(C_1-C_8 alkylenyl);

3- to 6-membered heterocycloalkyl;

Substituted 3- to 6-membered heterocycloalkyl;

3- to 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl);

Substituted 3- to 6-membered heterocycloalkyl-(C_1-C_8 alkylenyl)

HO;

(C_1-C_6 alkyl)-O;

H_2N;

(C_1-C_6 alkyl)-N(H);

(C_1-C_6 alkyl)$_2$-N;

Each substituted R^3 and R^4 group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

H_2N;

C_1-C_6 alkyl;

CN;

CF_3;

(C_1-C_6 alkyl)-OC(O);

HO;

(C_1-C_6 alkyl)-O;

HS; and

(C_1-C_6 alkyl)-S;

wherein each substituent on a carbon atom may further be independently selected from:

Halo; and

HO_2C;

wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;

R^5 is H, C_1-C_6 alkyl, H_2N, HO, or halo;

n is an integer of from 0 to 3;

Q is selected from:

OC(O);

$CH(R^6)C(O)$;

$OC(NR^6)$;

$CH(R^6)C(NR^6)$;

$N(R^6)C(O)$;

$N(R^6)C(S)$;

$N(R^6)C(NR^6)$;

$N(R^6)CH_2$;

SC(O);

$CH(R^6)C(S)$;

$SC(NR^6)$;

trans-(H)C=C(H);

cis-(H)C=C(H);

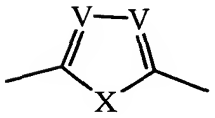
C≡C;

$CH_2C{\equiv}C$;

$C{\equiv}CCH_2$;

$CF_2C{\equiv}C$; and

$C{\equiv}CCF_2$;



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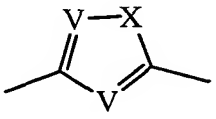

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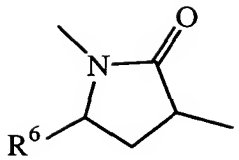

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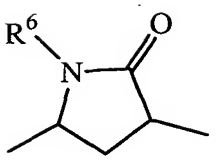

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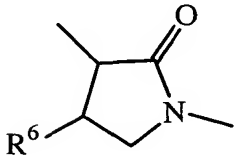

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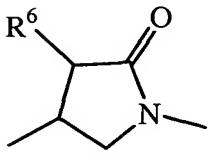

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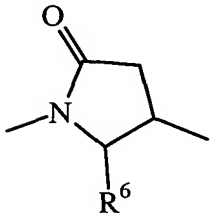

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R^6 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl; 3- to 6-membered heterocycloalkyl; phenyl; benzyl; or 5- or 6-membered heteroaryl;

X is O, S, N(H), or N(C_1-C_6 alkyl);

Each V is independently C(H) or N;

Y is C(=O), CH_2; C(H)(R^7), C(R^7)$_2$; O; S; S(O); or S(O)$_2$;

Each R^7 is independently C_1-C_6 alkyl, H_2N; HO; or halo;

---- means a bond which is optionally present or absent;

W^1 is independently N-R^5 or C(H)R^5 when ---- is absent, wherein R^5 is as defined above;

W^1 is independently N or C-R^5 when ---- is a bond, wherein R^5 is as defined above;

Each W^2, W^3, and W^4 is independently N or C-R^5, wherein R^5 is as defined above;

wherein at least 1 of W^1, W^2, W^3, and W^4 is N;

wherein each C_8-C_{10} bicycloalkyl is a bicyclic carbocyclic ring that contains 8-, 9-, or 10-member carbon atoms which are 5,5-fused, 6,5-fused, or 6,6-fused bicyclic rings, respectively, and wherein the ring is saturated or optionally contains one carbon-carbon double bond;

wherein each 8- to 10-membered heterobicycloalkyl is a bicyclic ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 S(O)$_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond, and wherein the heterobicycloalkyl is a 5,5-fused, 6,5-fused, or 6,6-fused bicyclic ring, respectively,

wherein each heterocycloalkyl is a ring that contains carbon atoms and from 1 to 4 heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 S(O)$_2$, 1 N, 4 N(H), and 4 N(C_1-C_6 alkyl), and wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C_1-C_6 alkyl), and 5- and 6-membered heteroaryl are monocyclic rings;

wherein each heterobiaryl contains carbon atoms and from 1 to 4 heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C_1-C_6 alkyl), and 4 N, and where the 8-, 9-, and 10-membered heterobiaryl are 5,5-fused, 6,5-fused, and 6,6-fused bicyclic rings, respectively, and wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

wherein with any (C_1-C_6 alkyl)$_2$-N group, the C_1-C_6 alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl;

wherein each group and each substituent recited above is independently selected; and

wherein the compound named 4-[1-oxo-7-(3-[1,2,3]triazol-1-ylprop-1-ynyl)-1H-isoquinolin-2-ylmethyl]benzoic acid is excluded.

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is C(=O) or CH_2.

3. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is O, S, S(O), or S(O)$_2$.

4. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is N(R^6)C(O).

5. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is C≡C, CH_2C≡C, C≡CCH_2, CF_2C≡C, or C≡CCF_2.

6. The compound according to Claim 1, wherein W^3 or W^4 is N and Q is N(H)C(O).

7. The compound according to any one of Claims 1 to 6, wherein R^1 and R^2 are independently selected from:
5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);
Substituted 5- or 6-membered heteroaryl-(C_1-C_8 alkylenyl);
8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);
Substituted 8- to 10-membered heterobiaryl-(C_1-C_8 alkylenyl);
Phenyl-(C_1-C_8 alkylenyl); and
Substituted phenyl-(C_1-C_8 alkylenyl).

8. The compound according to Claim 1, selected from:
4-[1-Oxo-7-(3-phenyl-prop-1-ynyl)-1H-3-azaisoquinolin-2-ylmethyl]benzoic acid tert-butyl ester;
4-[1-Oxo-7-(3-phenyl-prop-1-ynyl)-1H-3-azaisoquinolin-2-ylmethyl]benzoic acid;
2-(3,5-Difluoro-4-hydroxybenzyl)-7-[3-(4H-[1,2,3]triazol-4-yl)prop-1-ynyl]-2H-3-azaisoquinolin-1-one;
7-(3-Phenyl-prop-1-ynyl)-2-(4-trifluoromethylbenzyl)-2H-5-azaisoquinolin-1-one;
2-(3-Fluorobenzyl)-7-(3-phenyl-prop-1-ynyl)-2H-5-azaisoquinolin-1-one;
4-[7-(3-Imidazol-1-ylprop-1-ynyl)-1-oxo-1H-5-azaisoquinolin-2-ylmethyl]benzoic acid tert-butyl ester;
4-[7-(3-Imidazol-1-ylprop-1-ynyl)-1-oxo-1H-5-azaisoquinolin-2-ylmethyl]benzoic acid;
3-[1-Oxo-7-(3-phenyl-prop-1-ynyl)-1H-6-azaisoquinolin-2-ylmethyl]benzonitrile;
4-[1-Oxo-7-(3-phenyl-prop-1-ynyl)-1H-6-azaisoquinolin-2-ylmethyl]benzenesulfonamide;
4-[1-Oxo-7-(3-[1,2,3]triazol-1-ylprop-1-ynyl)-1H-6-azaisoquinolin-2-ylmethyl]benzoic acid tert-butyl ester;

4-[1-Oxo-7-(3-[1,2,3]triazol-1-ylprop-1-ynyl)-1H-6-azaisoquinolin-2-ylmethyl]benzoic acid;

4-[1-Oxo-7-(3-phenyl-prop-1-ynyl)-1H-8-azaisoquinolin-2-ylmethyl]benzoic acid methyl ester;

3-[1-Oxo-7-(3-phenyl-prop-1-ynyl)-1H-8-azaisoquinolin-2-ylmethyl]benzoic acid methyl ester;

2-(4-Fluorobenzyl)-7-3-phenylprop-1-ynyl-2H-3,5-diazaisoquinolin-1-one;

7-(3-Phenylprop-1-ynyl)-2-(3-trifluoromethylbenzyl)-2H-3,6-diazaisoquinolin-1-one;

2-(3-Chlorobenzyl)-7-(3-phenylprop-1-ynyl)-2H-3,8-diazaisoquinolin-1-one;

2-(3,4-Difluorobenzyl)-7-(3-phenylprop-1-ynyl)-2H-5,8-diazaisoquinolin-1-one; and

4-[1-Oxo-7-(3-[1,2,4]triazol-1-ylprop-1-ynyl)-1H-3,5,8-triazaisoquinolin-2-ylmethyl]benzoic acid tert-butyl ester; or

a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition, comprising a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

10. The pharmaceutical composition according to Claim 9, comprising a compound according to Claim 8, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.

11. A method for treating osteoarthritis or rheumatoid arthritis, comprising administering to a patient suffering from osteoarthritis a nontoxic effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

12. The method according to Claim 11, wherein the compound administered is a compound according to Claim 8, or a pharmaceutically acceptable salt thereof.

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